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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/812,113	03/15/2001	K. Roger Aoki	17006CON1	8430

7590 05/17/2002

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EXAMINER	
CHERNYSHEV, OLGA N	

ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 05/17/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/812,113	AOKI ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 11-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 11-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other.

DETAILED ACTION

Response to Amendment

1. Claims 1, 4 and 11-19 have been amended as requested in the amendment of Paper No.7, filed on March 07, 2002. Claims 1, 4 and 11-19 are pending in the instant application.

2. The Text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed on March 07, 2002 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 112

5. Claims 1, 4 and 11-19 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record specifically addressed in section 4 of Paper No.6.

Applicant submits that the term "neuromuscular disorders" is related to "numerous disorders of muscle innervation" (see section II of the Response) and the term is widely used by Internet users as well as in peer-reviewed journals (section III of the Response). Applicant further argues that "although "neuromuscular disorders" is a broad term it correctly describes the broad therapeutic value of botulinum toxin, since, as stated, botulinum toxin has in fact been

used to treat a broad variety of "neuromuscular disorders" (section IV). It is the Examiner's position that, although it is true that botulinum toxin has been shown to be useful in treatment of different disorders associated with dysfunction of muscle innervation, the instant specification is not found to be enabling for the use of botulinum toxin type A followed by the administration of botulinum type B for any "neuromuscular disorder". As it was explained in the section 4 of Paper No.6, the term "neuromuscular disorders" is so wide-ranging that it includes, for example, disorders of neuromuscular junction, e.g. myasthenia gravis (see Merck Manual, pages 1449-1551, 1420-1421, reference provided in the previous office action). Myasthenia gravis is a disease characterized by episodic muscle weakness caused by autoimmune attack on the acetylcholine receptor of the postsynaptic neuromuscular junction. The condition is improved by administration of cholinesterase-inhibiting drugs. The known mechanism of botulinum toxin action, in contrast, is directed to presynaptic cholinergic nerve terminals where it causes the inhibition of acetylcholine release and, consequently, muscular relaxation. One skilled in the art would not expect that administration of botulinum toxin type A followed by the administration of botulinum toxin type B would lead to the treatment of myasthenia gravis, a neuromuscular disorder. On the contrary, one skilled in the art would anticipate aggravation of the symptoms of myasthenia gravis after administration of botulinum toxin type A (or B). Thus, it would require undue experimentation for a skilled artisan to discover how to practice the present invention as currently claimed.

Applicant further submits (section V of the Response) that the instant specification provides enough guidance how to carry out the present invention. The attention is drawn to Example 1 and pages 9-10, and also to the fact that administration of botulinum toxin for

treatment of muscular spasms is known in the prior art. However, the instant invention is directed to the method of treating a neuromuscular disorder by administration of two different serotypes of botulinum toxins, A and B. The invention also encompasses method steps where development of neutralizing antibodies in response to the administration of botulinum toxin occurs. The instant specification fails to describe how to practice the claimed method. It is not clear and is not explained how to approximate the proper time when a patient experiences loss of clinical response to botulinum toxin type A and to begin administration of botulinum toxin of type B. It is also not apparent what is the therapeutically effective amount of the second administration. The instant specification (pages 9-10 or working Examples 1 and 2) does not provide any support for the estimation of development of neutralizing antibodies. Moreover, there is no scientific clarification given to the fact that, in effect, neutralizing antibodies to botulinum toxins type A might cross-react with and neutralize botulinum toxin type B as well. Because the instant specification fails to supply any working examples of the claimed method, one skilled in the art would have to resort to undue experimentation to discover how to practice the Applicant's invention as currently claimed.

6. Claims 1, 4, 11-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1, 4, 12 and 16 are indefinite and ambiguous because it is not clear and cannot be determined form the claims what is "therapeutically effective amount" of botulinum toxins type A and B for the reasons provided earlier. Briefly, the claimed method encompasses treatment with botulinum toxin A and B. Applicant's reference to the doses established in prior art is not

found to be persuasive because it is not clear and not shown by the instant specification what is the "therapeutically effective amount" of the toxins types A and B when practicing the claimed method.

8. Claims 11, 13, 16 and 17 are indefinite for being dependent form the indefinite claims.

Conclusion

9. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (703) 305-1003. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (703) 308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 782-9306 for regular communications and (703) 782-9307 for After Final communications.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 308-4556 or (703) 308-4242. If either of these numbers is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Official papers should NOT be faxed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Olga N. Chernyshev, Ph.D. OC
May 15, 2002

JOHN ULM
PRIMARY EXAMINER
1600